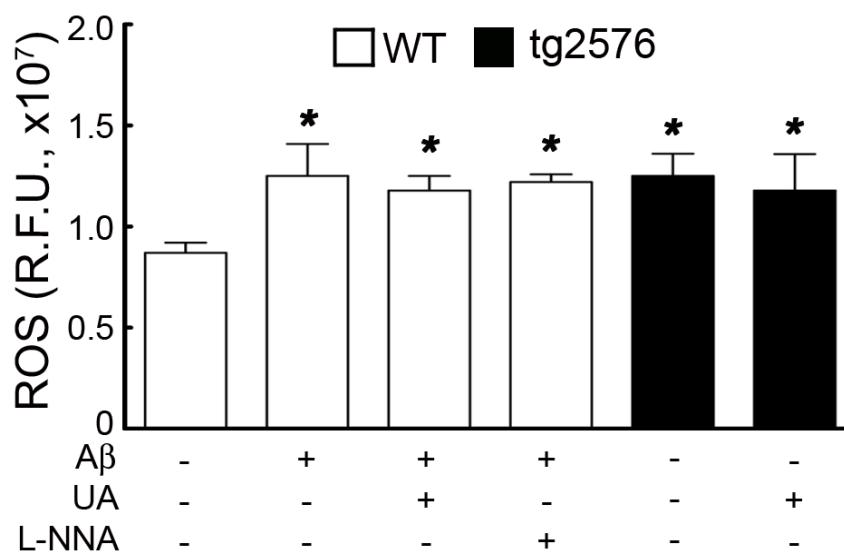
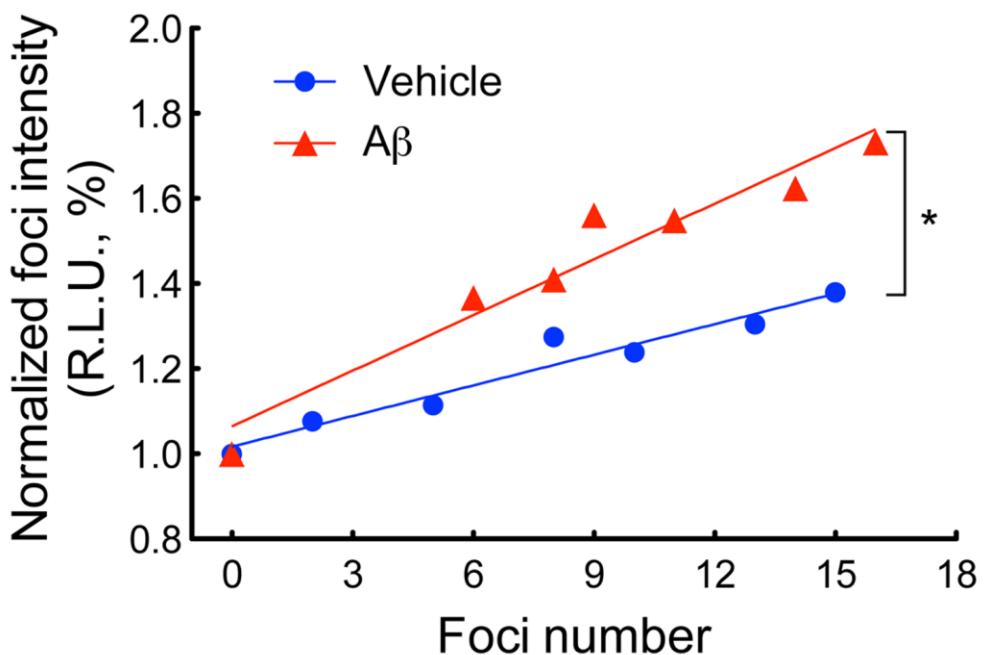


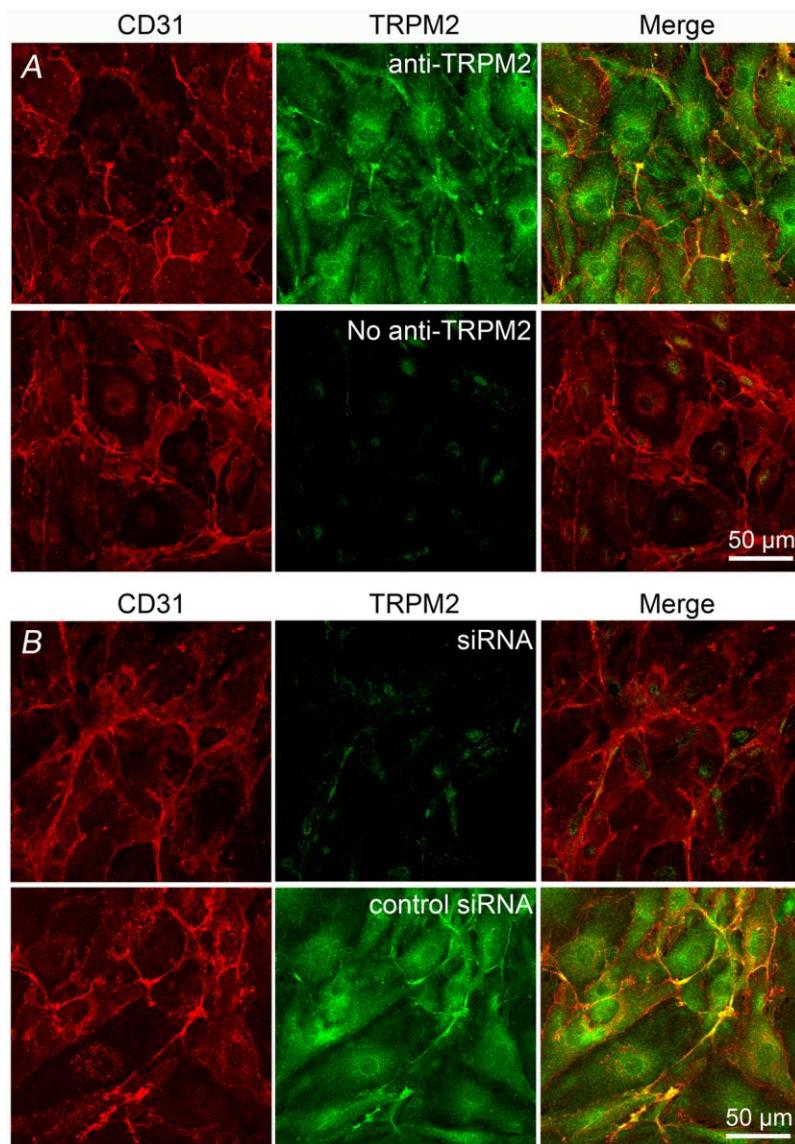
Supplementary Figure 1: Vascular nitrosative stress mediates the vasomotor dysfunction induced by A β . (A) Effect of neocortical application of the peroxynitrite scavenger UA or the peroxynitrite decomposition catalyst FeTPPS or its inactive control compound TPPS on the increase in CBF produced by the NO donor SNAP or hypercapnia. (B) Effect of neocortical application of the PARG inhibitor PJ34 on the increase in CBF induced by SNAP or hypercapnia, or the PARG inhibitor ADP-DPH on the increase in CBF induced by hypercapnia. Data are shown as mean \pm SEM. *p<0.05 from control; analysis of variance and Tukey's test; n=5/group.



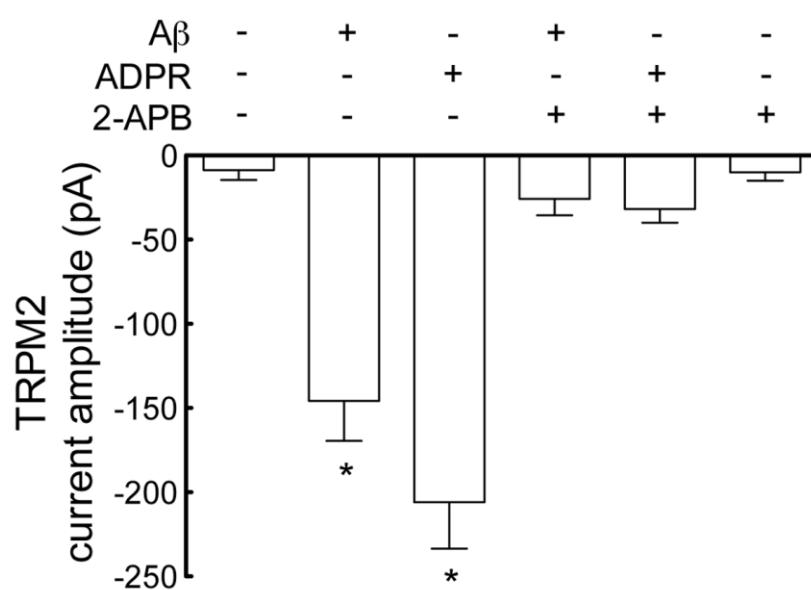
Supplementary Figure 2: Effect of neocortical application of the peroxynitrite scavenger UA or the NOS inhibitor L-NNA on ROS production induced by topical application of $\text{A}\beta_{1-40}$ ($\text{A}\beta$) in WT mice or observed in tg2576 mice. ROS produced was assessed by in situ HE microfluorography. Data are shown as mean \pm SEM. * $p<0.05$ from control; analysis of variance and Tukey's test;



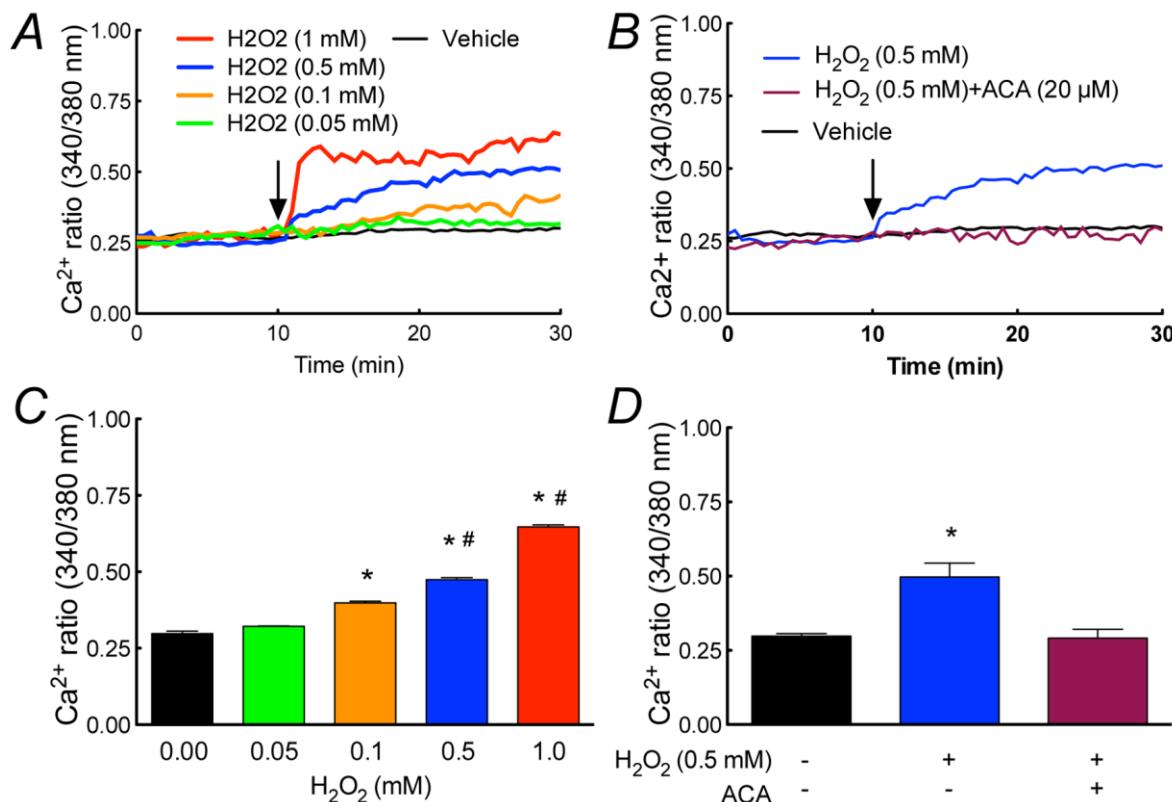
Supplementary Figure 3: Quantification of γ H2AX immunocytochemistry foci number (x axis) and intensity (y axis) in brain endothelial cells. There is a linear correlation between foci intensity and number (Pearson's correlation, $r^2=0.95$ for vehicle and $r^2=0.94$ for A β ; * $p<0.05$ between groups, two-tailed t-test). A β_{1-40} (A β) (300nM) increased both the intensity and the number of foci resulting in a significant increase in the slope of the relationship ($p<0.05$; n=20-30 cells in 3 separate experiments).



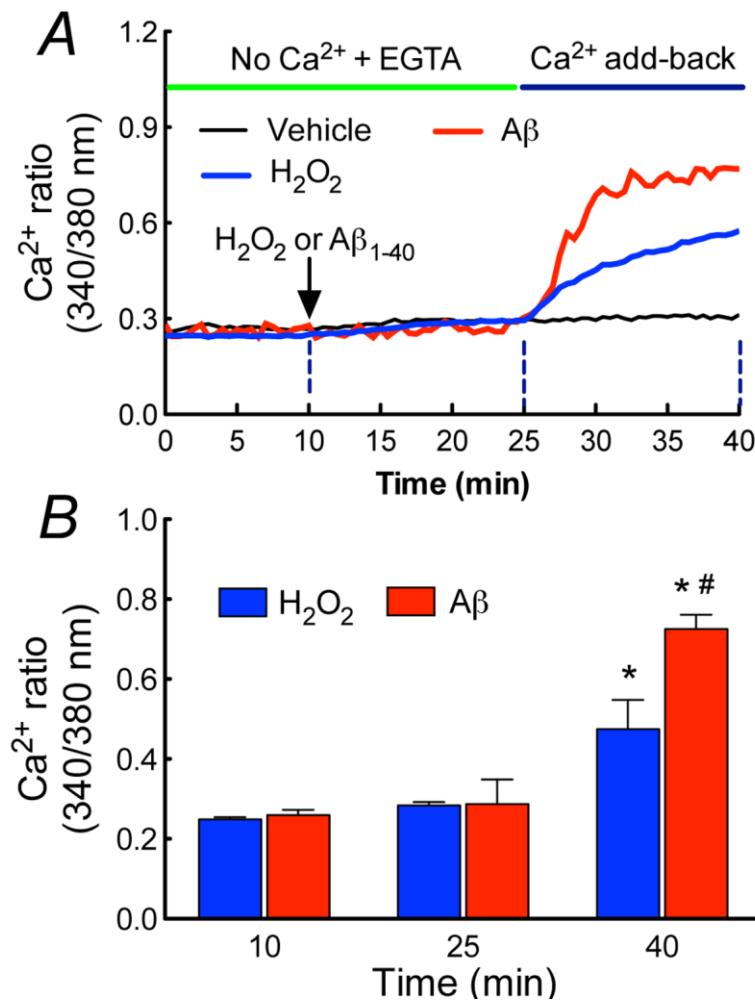
Supplemental Figure 4: Specificity of the TRPM2 antibody in brain endothelial cell cultures (bEND cells). The TRPM2 immunoreactivity is abolished by omission of the primary antibody (A) or in TRPM2 knockdown using siRNA (B).



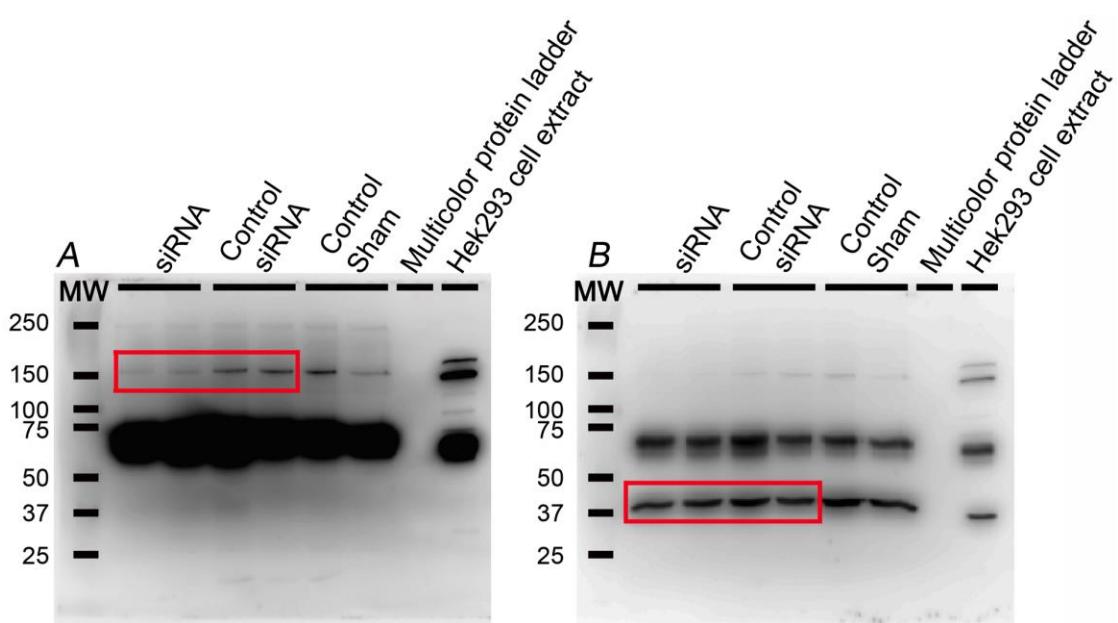
Supplemental Figure 5: The TRPM2 inhibitor 2-APB blocks the TRPM2 currents induced by A β_{1-40} (A β) or ADPR. Data are shown as mean \pm SEM. n=4-24 cells; *p<0.05 from no treatment.



Supplemental Figure 6: The TRPM2 channel activator H_2O_2 increases intracellular Ca^{2+} in endothelial cells. H_2O_2 increases intracellular Ca^{2+} dose-dependently (A,C). The increase in Ca^{2+} is blocked by the TRPM2 channel antagonist ACA (B,D). Data are shown as mean \pm SEM. * $p<0.05$ from 0.0 mM or vehicle; # $p<0.05$ from 0.1 or 0.5 mM; analysis of variance and Tukey's test.



Supplemental Figure 7: The increase in intracellular Ca^{2+} induced by $\text{A}\beta_{1-40}$ or H_2O_2 is dependent on extracellular Ca^{2+} . The increase in intracellular Ca^{2+} induced by $\text{A}\beta_{1-40}$ ($\text{A}\beta$, 300 nM) or H_2O_2 (0.5 mM) is not observed in Ca^{2+} -free medium with EGTA (10 mM) (A). Adding Ca^{2+} (2 mM) back leads to an increase in intracellular Ca^{2+} , suggesting that the source of Ca^{2+} is extracellular. Group data are shown in (B). Data are shown as mean \pm SEM. *p<0.05 from 10 or 25 min; **p<0.05 from H_2O_2 ; n=10-15 cells in 3 separate experiments; Analysis of variance and Tukey's test.



Supplemental Figure 8: Full scan images of Western blot. Full blots for Figure 5C (A,B). Crop areas are highlighted in red.

Supplementary Table 1. Physiological variables

	Genotype	Treatment	Stimuli	N	MAP (mmHg)	pCO ₂ (mmHg)	pO ₂ (mmHg)	pH
Fig. 1	WT	No treatment	Whisker, ACh, Adenosine	5	81±3	30.5±1.5	133.5±5.0	7.42±0.01
			Hypercapnia	5	83±3	56.0±1.3*	138.4±6.4	7.22±0.02*
		A β	Whisker, ACh, Adenosine	5	83±4	32.2±2.2	129.3±2.5	7.41±0.02
			Hypercapnia	5	83±4	55.2±1.0*	128.1±8.3	7.23±0.02*
		A β +FeTPPS	Whisker, ACh, Adenosine	5	84±2	33.5±2.3	129.2±6.0	7.36±0.02
			Hypercapnia	5	84±1	53.1±2.1*	130.4±3.4	7.21±0.01*
		A β +TPPS	Whisker, ACh, Adenosine	5	83±1	34.4±3.1	131.9±6.0	7.36±0.01
			Hypercapnia	5	83±1	54.6±4.1*	132.3±3.8	7.19±0.03*
		A β +UA	Whisker, ACh, Adenosine	5	82±3	34.1±1.3	133.9±9.7	7.39±0.01
			Hypercapnia	5	81±2	57.0±2.2*	130.0±6.2	7.18±0.03*
		FeTPPS	Whisker, ACh, Adenosine	5	84±3	35.1±1.6	133.9±6.8	7.39±0.03
			Hypercapnia	5	84±2	56.7±2.8*	136.1±6.2	7.19±0.02*
		TPPS	Whisker, ACh, Adenosine	5	86±4	35.4±2.5	127.1±5.0	7.36±0.03
			Hypercapnia	5	86±2	55.5±1.3*	129.4±7.9	7.21±0.02*
		UA	Whisker, ACh, Adenosine	5	84±2	33.5±2.6	131.6±6.5	7.37±0.02
			Hypercapnia	5	85±1	54.3±2.7*	133.4±3.6	7.19±0.02*

Mean±SEM; *p<0.05 vs normocapnia

Supplementary Table 2. Physiological variables.

	Genotype	Treatment	Stimuli	N	MAP (mmHg)	pCO ₂ (mmHg)	pO ₂ (mmHg)	pH
Fig. 2	PARP1 ^{+/+}	No treatment	Whisker, ACh, Adenosine	5	83±2	31.7±0.7	130.9±3.0	7.40±0.01
			Hypercapnia	5	84±3	53.3±0.8*	134.4±2.5	7.24±0.01*
		Aβ	Whisker, ACh, Adenosine	5	83±5	33.9±1.7	125.4±3.0	7.40±0.03
			Hypercapnia	5	82±6	55.0±1.4*	127.0±5.4	7.22±0.02*
		Aβ+PJ34	Whisker, ACh, Adenosine	5	80±3	34.4±2.2	127.8±5.6	7.37±0.02
			Hypercapnia	5	79±5	56.5±1.6*	131.8±2.1	7.18±0.03*
		PJ34	Whisker, ACh, Adenosine	5	83±5	34.2±1.5	126.9±6.8	7.40±0.02
			Hypercapnia	5	83±7	55.9±1.5*	133.3±2.0	7.20±0.04*
		Aβ+ADP- HPD	Whisker, ACh, Adenosine	5	85±5	30.5±1.7	132.0±6.2	7.42±0.02
			Hypercapnia	5	84±3	55.2±2.0*	124.9±7.2	7.21±0.03*
		ADP-HPD	Whisker, ACh, Adenosine	5	85±5	29.5±2.1	128.1±7.6	7.41±0.02
			Hypercapnia	5	85±3	53.0±1.9*	133.8±3.2	7.24±0.02*
	PARP1 ^{-/-}	No treatment	Whisker, ACh, Adenosine	5	83±3	32.3±1.7	132.5±7.0	7.41±0.01
			Hypercapnia	5	83±3	56.3±1.3*	136.1±7.2	7.25±0.02*
		Aβ	Whisker, ACh, Adenosine	5	84±5	30.8±1.0	134.9±8.4	7.39±0.01
			Hypercapnia	5	83±4	56.5±1.4*	127.9±7.9	7.22±0.02*

Mean±SEM; *p<0.05 vs normocapnia

Supplementary Table 3. Physiological variables.

	Genotype	Treatment	Stimuli	N	MAP (mmHg)	pCO ₂ (mmHg)	pO ₂ (mmHg)	pH
Fig. 3	WT	No treatment	Whisker, ACh, Adenosine	5	82±2	32.4±1.4	130.8±4.0	7.37±0.01
			Hypercapnia	5	80±2	51.2±1.4*	137.6±3.1	7.20±0.02*
		PJ34	Whisker, ACh, Adenosine	5	82±2	33.2±1.3	132.7±3.0	7.36±0.01
			Hypercapnia	5	79±3	52.9±1.3*	134.6±4.5	7.19±0.03*
		ADP-HPD	Whisker, ACh, Adenosine	5	86±5	29.5±1.6	130.3±4.5	7.40±0.01
			Hypercapnia	5	85±3	51.6±1.6*	131.4±3.6	7.25±0.02*
	tg2576	No treatment	Whisker, ACh, Adenosine	5	82±4	33.4±1.2	129.7±4.3	7.39±0.01
			Hypercapnia	5	82±3	55.8±1.8*	135.7±5.6	7.18±0.03*
		PJ34	Whisker, ACh, Adenosine	5	83±4	33.3±1.6	128.5±5.5	7.39±0.01
			Hypercapnia	5	83±3	53.9±2.0*	132.2±3.9	7.24±0.03*
		ADP-HPD	Whisker, ACh, Adenosine	5	85±5	31.5±1.9	135.5±5.0	7.39±0.01
			Hypercapnia	5	83±2	54.2±2.4*	131.3±6.0	7.25±0.01*

Mean±SEM; *p<0.05 vs normocapnia

Supplementary Table 4. Physiological variables.

	Genotype	Treatment	Stimuli	N	MAP (mmHg)	pCO ₂ (mmHg)	pO ₂ (mmHg)	pH
Fig. 7	WT	No treatment	Whisker, ACh, Adenosine	5	83±3	32.3±2.2	130.1±5.9	7.40±0.02
		Abeta		5	85±3	32.3±2.2	130.1±6.2	7.40±0.02
		Aβ+2-APB		5	85±3	34.9±1.9	130.0±5.9	7.37±0.02
		2-APB		5	84±2	33.6±1.5	130.1±5.3	7.38±0.02
		Aβ+ACA		5	83±3	36.3±1.7	134.7±6.2	7.37±0.01
		ACA		5	83±1	35.7±0.9	133.7±4.4	7.37±0.01
	tg2576	No treatment	Whisker, ACh, Adenosine	5	83±2	34.0±1.8	130.2±4.3	7.38±0.01
		2-APB		5	82±2	34.9±2.3	130.8±3.0	7.40±0.02
		ACA		5	81±4	32.0±1.5	132.0±5.5	7.37±0.02

Supplementary Table 5. Physiological variables.

	Genotype	Treatment	Stimuli	N	MAP (mmHg)	pCO ₂ (mmHg)	pO ₂ (mmHg)	pH
Fig. 8	TRPM2 ^{+/+}	Vehicle	Whisker, ACh, Adenosine	5	85±2	29.3±1.7	137.0±5.7	7.41±0.02
		Aβ		5	84±2	32.1±2.2	134.8±7.1	7.38±0.02
		Vehicle		5	85±2	30.3±1.4	129.3±3.6	7.38±0.01
		Aβ		5	87±2	32.4±1.3	129.9±4.5	7.37±0.01
	TRPM2 ^{-/-}	Vehicle	Whisker, ACh, Adenosine	5	85±2	29.3±1.7	137.0±5.7	7.41±0.02
		Aβ		5	84±2	32.1±2.2	134.8±7.1	7.38±0.02
		Vehicle		5	85±2	30.3±1.4	129.3±3.6	7.38±0.01
		Aβ		5	87±2	32.4±1.3	129.9±4.5	7.37±0.01